Remarks

In the official action, the examiner has rejected claims 27-29, 31-39, and 41-43 as obvious over Simpson '643 in view of Thastrop '021.

As explained previously, the Simpson '643 patent relates to a bioluminescent bioreporter integrated circuit. This device is an integrated circuit which contains a photodetector (in addition to other components of the integrated circuit). A layer of polymer matrix containing a "reporter" material which emits light when it is contacted with a substance being detected is located in suitable proximity to the surface of the photodetector, separated from it by a transparent layer of biocompatible bioresistant material. When a substance to be detected comes into contact with the polymer layer and hence ultimately with the "reporter" material, light is emitted by the "reporter" material and detected by the adjacent photodetector, the size of the photodetector signal being proportional to the concentration of the material being detected. Several embodiments of the Simpson device are disclosed, but each operates in the manner discussed above.

In their previous response to a rejection for anticipation, the applicants pointed out that Simpson does not disclose any possibility for detecting a spatial distribution of signals produced when a substance which causes the biological sensor material to produce a signal comes into contact with a spatially discrete area of the sheet of diffusion-controlling matrix which contains the biological sensor material.

In the official action, the examiner responded, "Simpson et al fail to teach a means for detecting the spatial distribution of signals produced when the substance is in contact with at least one spatially-discrete area of the sheet of the polymer matrix." This is correct, and applicants would now argue further that in view of the integrated circuit design and intended uses for the Simpson probe, the Simpson reference does not contemplate any possibility for a substance which is to be detected to come into contact with a spatially-discrete area of the sheet of polymer matrix on the integrated circuit probe.

Furthermore, Simpson teaches that the polymer matrix holds the reporter material, and is permeable to the substance to be detected so that the substance to be detected can reach the

reporter material and be detected. However, as Simpson does not contemplate bringing the substance to be detected into contact with any spatially-discrete areas of the polymer matrix, and does not contemplate detecting the spatial distribution of signal(s) produced if the substance to be detected were brought into contact with spatially-discrete areas of the polymer matrix, Simpson does not contemplate or require the polymer matrix to be diffusion-controlling.

In the official action, the examiner states that "Simpson et al specifically teach encapsulated cells that can be formed into sheets or thickness or diameter desired, where cells may be added to molten agar or agarose, where gelation occurs as the agar or agarose cools to room temperature (column 68, lines 33-51)." Applicants respond that the complete statement on the form which the encapsulated cells may take is, "Encapsulated cells can be formed into sheets or beads, almost of any thickness or diameter desired, depending on the method chosen. The small area available for cell deposition on an integrated circuit requires thin sheets (0.1-2 mm) or small diameter beads (<50 μm) to be produced." See column 68, lines 37-41. This is a teaching that thin sheets or small diameter beads of the matrix are needed for deposition on integrated circuits having small areas available for cell deposition. Large sheets of matrix are not suggested.

In the official action, the examiner has now cited the Thastrop '021 reference in combination with Simpson, and rejected the claims on grounds of obviousness. He argues that Thastrup teaches the monitoring and recording of quantitative information correlating the spatial distribution or change in the spatial distribution of cell luminescence, and further teaches that this makes it possible to set up meaningful relationships between the influences of a chemical substance or mixture of chemical substances on cellular systems and the redistribution response in both a fast and reproducible manner, and that therefore, "it would have been obvious in the device of Simpson et al to have a means for detecting the spatial distribution of signals produced when the substance is in contact with at least one spatially-discrete area of the sheet of the polymer matrix, as suggested by Thastrup et al, in order to make it possible to set up meaningful relationships between the influence of a chemical substance or mixture of chemical substances on cellular systems and the redistribution response in both a fast and reproducible manner." Applicants fail to see the logic in the examiner's argument.

Thastrup '021 deals with a "method for extracting quantitative information relating to an influence on a cellular response" (title). According to the abstract, cells are modified to express a luminophore.....coupled to a component of an intracellular signaling pathway. An "influence" modulates the intracellular signaling pathway in such a way the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of influence. Measurement of redistribution is performed by recording of light intensity (or other signal) by an apparatus consisting of e.g., a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution.

In Thastrup, the section entitled "Field of Invention" explains, "The present invention relates to a method and tools for extracting quantitative information relating to an influence, on a cellular response, in particular an influence caused by contacting or incubating the cell with a substance influencing a cellular response, where the cellular response is manifested in redistribution of at least one component in the cell. In particular, the invention relates to a method for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of a least one component associated with the pathway. The method of the invention may be used as a very efficient procedure for testing or discovering the influence of a substance on a physiological process, for example in connection with screening for new drugs, testing of substances for toxicity, identifying drug targets for known or novel drugs. Other valuable uses of the method and technology of the invention will be apparent to the skilled person on the basis of the following disclosure. In a particular embodiment of the invention, the present invention relates to a method of detecting intracellular translocation or redistribution of biologically active polypeptides, preferable an enzyme, affecting intracellular prosesses, and a DNA construct and a cell for use in the method."

Translated into plain English, the Thastrup '021 reference discloses cells that are modified to express a luminophore (a "tag" which emits light under certain conditions) which is coupled to a cellular component of an intracellular pathway. In the method of the reference, the cells are subjected to some sort of "influence" which affects the intracellular signaling pathway in a way which results in the luminophore-labeled cell component being moved within the cell as

a function of the degree of the "influence" to which the cell was subjected. The microscope-based detection system then can follow the movement of the labeled cell component within the cell by observing the movement of the luminophore. The bottom line is that movements of tagged cell components within living cells can be observed and quantitated employing a microscope-based detection system. The examiner employs the Thastrup '021 reference for its disclosure of a detection system which is capable of detecting a spatial distribution of signals from a small-scale source.

There is no suggestion to combine the teachings of the Simpson '643 and Thastrup '021 references, and the presently-claimed system is not produced if the references are combined as the examiner suggests. Combining the microscope-based detection system of Thastrup with the bioreporter integrated circuit of Simpson would produce an instrument having an integrated circuit containing a photodetector which bears a layer of "reporter" material separated from the photodetector by a transparent layer of biocompatible bioresistant material, and in addition, a second detection system employing a microscope coupled to a suitable digital camera. Given that the purpose of the Simpson device is use as a probe for detecting and quantitating various trace substances in "inhospitable areas" such as groundwater, industrial process vessels, and battlefields (see the abstract), it is clear that the addition of a microscope-based second detection system is not only utterly superfluous but counterproductive. In other words, the addition of a microscope-based second detection system to the Simpson device would completely negate its intended utility. In addition, there is no provision in the suggested combination for bringing any substance (which is to be detected) into contact with any spatially-discrete area of the sheet of the Simpson "reporter" material on the integrated circuit.

Alternatively, if the basis for the examiner's rejection is a conclusion that it is obvious to modify the Simpson device by discarding the integrated circuit portion of Simpson's probe and retaining only the remaining (tiny) sheet of polymer matrix which contains reporter material, and then employing the microscope-based detection system of Thastrup to detect signal(s) emitted when a substance to be detected comes into contact with the polymer matrix sheet, this would clearly destroy the utility of the Simpson probe for its intended purpose, and would still not produce any spatial distribution of signals, because in the suggested combination there is no

suggestion or provision for bringing any substance (which is to be detected) into contact with any spatially-discrete area of the sheet of the Simpson "reporter" material.

Claims 28, 29, 31-39, and 41-43 were rejected on various grounds. These claims should be patentable as proper dependent claims referring to claim 27, if and when claim 27 is found to be patentable. Only if the examiner is able to make a proper rejection of claim 27 will it become necessary to consider the patentability of these dependent claims separately.

Claim 40 was rejected on the ground that determining the recited optical density of the sheet of diffusion-controlling matrix which contains the biological sensor material is a matter of routine skill in the art. Again, this is a proper dependent claim which should be patentable if and when independent claim 27 is found to be patentable.

Claim 30 was rejected under §103(a) as obvious over Simpson in view of Thastrup and further in view of Ribi '810. The Ribi reference is cited as disclosing polyacrylate properties which the examiner seems to think are relevant to the present invention. Applicants respond that the arguments presented above with respect to the Simpson and Thastrup references apply also to the rejection of claim 30. Claim 30 should be patentable as a proper dependent claim referring to independent claim 27 if and when the examiner finds claim 27 to be patentable. Only if the examiner is able to make a proper rejection of claim 27 will it be necessary to consider patentability of any of the dependent claims separately.

Respectfully submitted,

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